The Likely Role of Vitamin D from Solar Ultraviolet-B Irradiance in Increasing Cancer Survival

WILLIAM B. GRANT

Sunlight, Nutrition and Health Research Center (SUNARC), San Francisco, CA 94109-2529, U.S.A.

Abstract. *Background: Solar ultraviolet-B (UVB) and vitamin D have been found inversely correlated with cancer incidence, mortality, and survival rates in many studies. Materials and Methods: In this work, two sets of cancer data were used: age-adjusted cancer incidence and mortality rates in 2002 for 21 Western developed countries and cancer survival data from Eurocare-3 for nine European countries for cancer diagnosed from 1990 to 1994. The data were used in ecologic studies with respect to latitude, an index of solar UVB irradiance, and dietary supply factors for 1985. Results: Statistically significant correlations of effective or actual survival rates with increasing latitude were found for breast, colon, gastric, lung, ovarian, pancreatic, prostate and renal cancer, and non-Hodgkin's lymphoma. Five-year survival rates south of 50˚N were 20%–50% higher than those near 55˚N. Conclusion: These results provide additional support for an increase in cancer survival rates linked with natural vitamin D.*

Although smoking, alcohol consumption and dietary factors play a major role in the etiology of cancer (1, 2), there is increasing evidence that solar utraviolet-B (UVB) irradiance and vitamin D reduce the risk of cancer incidence or mortality (3-5). There is also mounting evidence that vitamin D increases the survival rate once cancer has been diagnosed. Studies in Norway found that the survival rates for breast, colon and prostate cancer and Hodgkin's lymphoma were 10%–30% higher if the diagnosis had been made in summer or fall rather than in winter or spring (6-8). A report from the Health Professionals Follow-up Study found that a vitamin D index was more strongly correlated with cancer mortality rates than incidence rates (9). A study in Boston found that 5-year survival from non–small cell lung cancer was twice as great after summer operation and high vitamin D intake compared to operation in winter and low vitamin D intake (10). A study suggested that the survival rates for black Americans diagnosed with cancer are lower than those for white Americans, in part because of lower vitamin D from solar UVB irradiance (11). These findings could have considerable public health implications since vitamin D is easily obtained through a combination of natural and artificial UVB irradiance, vitamin D-fortified food, fatty coldwater fish and supplements.

In this work, cancer incidence and mortality rates and their ratio for Western developed countries in 2002 were used in an ecological analysis with respect to latitude, an index for solar UVB irradiance and dietary supply factors. Data on survival rates for nine European countries for cancer diagnosed between 1990 and 1994 were used in an ecologic study with respect to latitude.

Correspondence to: William B. Grant, Sunlight, Nutrition and Health Research Center (SUNARC), 2107 Van Ness Avenue, Suite 403B, San Francisco, CA 94109-2529, U.S.A. Tel: 1-415-776-5274, Fax: 1-415-776-5270, e-mail: wgrant@sunarc.org / www.sunarc.org

Key Words: Alcohol, animal products, insulin-like growth factor-I (IGF-I), sugar, vegetables.

Materials and Methods

The ecologic approach is used to determine links between various risk-modifying factors and cancer mortality rates. The strengths and limitations of the ecologic approach have been previously reviewed (12, 13). The main strength of the ecologic approach is the ease of conducting the studies; the main weakness is that apparent associations may be due to unmodeled factors. Thus, ecologic studies should be followed by other studies. Generally, associations are examined between suspected risk or protective factors and disease outcomes. Once associations are found, further analyses are conducted to determine whether the associations satisfy standard criteria for causality (14, 15).

The ecologic approach has been used in many studies linking UVB to cancer risk reduction. It was used to make the first links between solar UVB irradiance and cancer risk reduction for colon (16, 17), breast (18-21), ovarian (22) and prostate (23) cancer. It has also been used to extend the number of vitamin D-sensitive cancers to 18 based on data in the Atlas of Cancer Mortality Rates (24, 3, 5, 25, 26) and European data (27). Whereas the first study in this set used only solar UVB irradiance for July (28) with data from the Atlas of Cancer Mortality Rates (24), the later studies included alcohol consumption, Hispanic heritage, poverty, smoking and urban residence. Dietary factors were not included since they did not vary widely during the periods studied (29). Prostate cancer was found to be associated with July UVB irradiance and with latitude, an index

0250-7005/2006 $2.00+.40

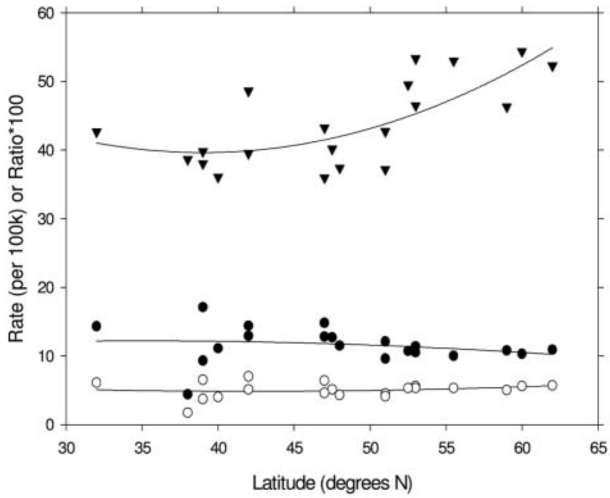

Figure 1. *Incidence (dots) and mortality (circles) rates and the ratio of mortality to incidence rates times 100 (triangles) for non-Hodgkin's lymphoma (NHL), males, for Western developed countries (32) vs. latitude.*

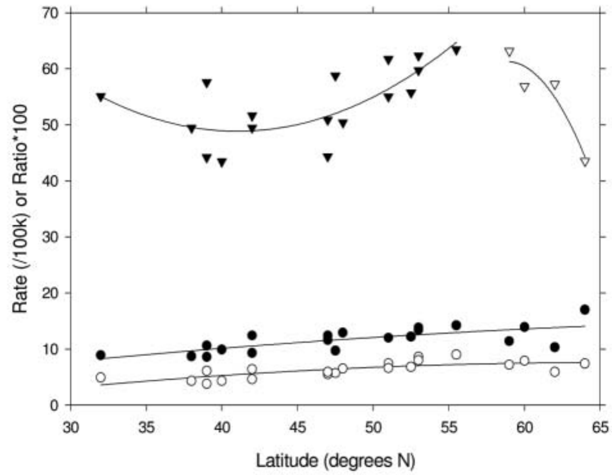

Figure 2. *Same as for Figure 1, but for ovarian cancer.*

for wintertime serum 25-hydroxyvitamin D (25(OH)D) (30), supporting an earlier study on serum 25(OH)D and the subsequent development of prostate cancer in Nordic countries (31).

Cancer data. One set of data on cancer incidence and mortality rates was obtained from GLOBOCAN 2002 (32). The 21 countries used in this study were as follows: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, The Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom and the United States. These countries were chosen since they have western European ethnic heritage, similar skin pigmentation, similar diets, and good health care systems. The ratio of mortality to incidence is used here as a proxy for survival rate. The data used are shown plotted against latitude in Figures 1-4. The ratio of mortality to incidence was multiplied by a factor of 100 for display purposes. Second-order fits to the data are provided as guides to the eye.

A second set of cancer survival data was obtained from a EUROCARE-3 report (33). The data were based on the survival of adult cancer patients diagnosed from 1990 to 1994 in European countries. Coverage ranged from 8% in Austria to 100% in several countries. European age-standardized relative 1- and 5-year survival rates (34) were given separately for men and women. The countries included were Austria (48˚N), Denmark (55.5˚N), England (52˚N), France (48˚N), Germany (51˚ N), Italy (42˚N), The Netherlands (52.5˚N), Spain (40˚N), and Switzerland (47˚N), where the latitudes indicated are near the population centers. There were 579,000 males and 550,000 females included in the data for these countries. The uncertainty of the survival estimates for some of the minor cancers for countries with low coverage was about 5%–10%.

The countries excluded from the EUROCARE-3 data set in this analysis were: (i) East European countries since medical care in those countries was different from that in western Europe; (ii) small countries since the number of cases was generally small in these countries; (iii) Nordic countries, because they must obtain vitamin D from sources other than the sun (35); and (iv) Portugal, since the 5-year survival rates appeared to be lower than could be explained on the basis of latitude, generally being 70%–90% of those of neighboring Spain.

Dietary supply data. Dietary supply data were obtained from the Food and Agriculture Organization (36). There is generally a 15- to 20-year lag between dietary factors and cancer diagnosis or death (37, 38). Thus, data for 1984–1986 were used in this study. The most important dietary risk factor for many types of cancer appears to be the fraction of energy derived from animal products (2, 38-41), whereas vegetable products such as fruits, vegetables and whole grains are generally risk reduction factors (2, 42, 43); however, some animal products, such as fish and milk, have sometimes been associated with reduced cancer risk (39, 44, 45). The probable mechanisms for risk associated with animal products include production of insulin-like growth factor-I (IGF-I) (46) and endogenous estrogen (47, 48). However, hormone replacement therapy has been associated with reduced risk of colon cancer (49). There may be other mechanisms related to the diet that explain the link to colon cancer (50). Other factors, such as alcohol, animal fat, cereals, fruit, milk and sugar, were also considered in the analyses.

Vitamin D can be obtained from solar and artificial UVB irradiance, diet and supplements. In European countries, diet and supplements provide a small proportion of the vitamin D except for the Nordic countries. In winter, serum 25(OH)D levels actually increased with increasing latitude (51). Several factors are involved in the photoproduction of vitamin D, including seasonal variation of solar UVB irradiance, latitude, skin pigmentation (35), time spent outdoors and urban/rural residence. In this work, latitude was used as the index of variation of serum 25(OH)D, in part because solar UVB seems to be a very important source of vitamin D, and in part because summertime UVB has been found associated with increased survival rates after the diagnosis of breast, colon and prostate cancer (6-10). It should be noted that solar UVB irradiance is also a function of surface elevation and stratospheric ozone levels, both of which contribute to a noticeable asymmetry in the United

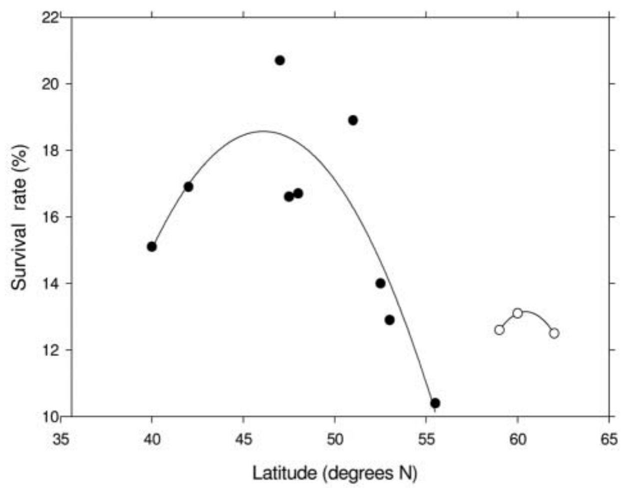

Figure 3. *Pancreatic cancer survival rates, males, for the period 1990-1994 (33) vs. latitude. West European countries between 40˚ and 56˚ N are indicated by dots, while Nordic countries are indicated by circles.*

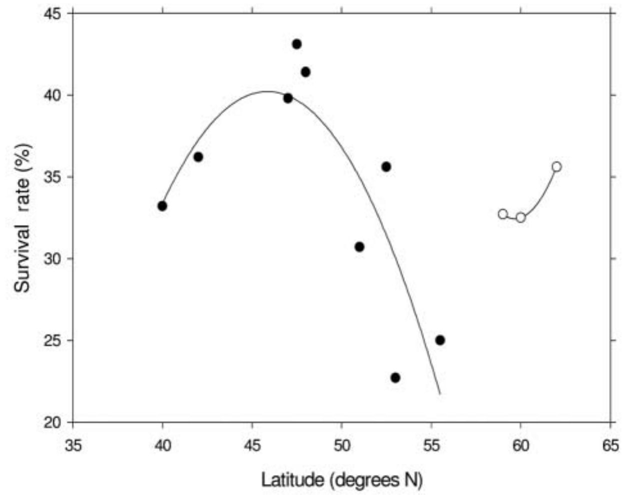

Figure 4. *Same as for Figure 3, but for lung cancer, in females.*

Table I. *Cross-correlation coefficients for the factors used in this study for the 17 Western developed countries.*

Factor	AE/TE 85 (adjusted r^2, *p*)	Fruit 85 (adjusted r^2, *p*)	Latitude (adjusted r^2, *p*)	Lat*Lat (adjusted r^2, *p*)	Sugar 85 (adjusted r^2, *p*)	T_{max} (adjusted r^2, *p*)
Alcohol 93	–0.06, 0.83	(–)0.15, 0.07	0.13, 0.09	0.13, 0.09	0.02, 0.26	(–)0.15, 0.07
AE/TE 85			0.17, 0.06	0.19, 0.05	0.34, 0.008	(–)0.46, *
Fruit 85			(–)0.07, 0.16	(–)0.09, 0.13	–0.06, 0.79	0.29, 0.02
Latitude				1.00, *	–0.06, 0.78	(–)0.56, *
Lat*Lat					–0.06, 0.73	(–)0.59, *
Sugar 85						(–)0.05, 0.19

*$p<0.001$; AE = energy derived from animal products; TE = total energy; Lat = latitude; Lat*Lat = latitude times latitude; T_{max} = maximum temperature for July; 85 = 1985; 93 = 1993; – = very poor correlation; (–) = inverse correlation.

States (28). However, for this study, latitude appeared to suffice, as most of the countries considered have populations mainly living at low elevations (except Austria and Switzerland).

Temperature. Ambient temperature may play a role in cancer risk, perhaps by affecting the amount and time of day that people spend outdoors, as well as the amount of clothing they wear. For this study, data for the average maximum temperature for July were obtained from the World Weather Information Service (http://www.worldweather.org, accessed September 16, 2005).

Statistical analysis. The data were used in linear-regression analyses employing SPSS Version 13.0 (52). The 17 non-Nordic countries were sometimes considered separately since much of the vitamin D in those countries comes from diet and supplements (35). Linear-regression analyses were performed on rates for incidence, mortality, and mortality divided by incidence.

The factors used in this ecologic study were more or less correlated with each other. The cross-correlation coefficients for the factors found to be most useful are presented in Table I for the 17 Western developed countries.

Results

The regression results for several cancers based on incidence and mortality data are given in Table II and Figures 1-2. It can be seen that, in some cases, diet had a stronger correlation than latitude and *vice versa* . Among the cancers investigated, five were found to have interesting latitudinal variations of incidence and/or mortality rates that could not be explained solely on the basis of dietary factors, namely breast, lung, ovarian and renal cancer and non-Hodgkin's lymphoma (NHL).

The regression results for the quadric fit to latitude for the EUROCARE-3 data are given in Table III and Figures 3-4. Statistically significant results were found for all: breast, colon, gastric, lung, pancreatic, prostate, and renal cancer. Most of the other cancers tabulated in (33) were examined for a statistically significant correlation with latitude with negative results.

Table II. *Regression results for year 2002 cancer incidence, mortality and mortality divided by incidence rates for 17 Western developed countries. Dietary data are for 1985 unless otherwise noted. The normalized regression coefficient is β and the significance is p. R is the correlation coefficient, and the F statistic is a measure of the contribution of the independent variables in predicting the dependent variable.*

Cancer, gender	First term (β, *p*)	Second term (β, *p*)	Third term (β, *p*)	Adjusted R^2, F, *p*
All except lung, M, Inc	–0.80, 0.001 Vegetables	–0.61, 0.006 Latitude		0.54, 10, 0.002
All except lung, M, Mor.	–0.74, 0.001 T_{max}	–0.63, 0.003 Sugar		0.58, 12, 0.001
All except lung, M, Mor/Inc	–0.95, 0.001 T_{max}	0.78, 0.007 Vegetables	–0.50, 0.01 Sugar	0.73, 15, *
Breast, F, Inc	0.67, 0.003 AE/TE			0.41, 12, 0.003
Breast, F, Mor	–0.59, 0.008, T_{max}	0.36, 0.08 Lat*Lat		0.78, 29, *
Breast, F, Mor/Inc	0.66, 0.02 Lat*Lat	–0.39, 0.14 AE/TE		0.25, 3.6, 0.05
Breast, F, Mor/Inc (Port out)	0.56, 0.03 Lat*Lat			0.26, 6.3, 0.03
Colorectal, M, Inc	–0.63, 0.05 Lat*Lat	–0.67, 0.09 T_{max}	0.47, 0.09 AE/TE	0.46, 5.6, 0.01
Colorectal, M, Inc	–0.82, 0.03 T_{max}	–0.55, 0.10 Lat*Lat	0.36, 0.10 Sugar	0.46, 5.5, 0.01
Colorectal, M, Mor	–0.73, 0.001 T_{max}			0.50, 17, 0.001
Colorectal, M, Mor/Inc	–0.70, 0.002 Sugar	5.94, 0.03 Lat*Lat	–5.57, 0.04 Latitude	0.52, 7.0, 0.005
Colorectal, F, Inc	0.50, 0.03 Sugar	0.37, 0.01 AE/TE		0.57, 11, 0.001
Colorectal, F, Mor	0.60, 0.02 AE/TE	0.17, 0.46 Lat*Lat		0.41, 6.5, 0.01
Colorectal, F, Mor/Inc	0.50, 0.02 Alcohol 93	–0.43, 0.04 Sugar		0.50, 8.9, 0.003
Esophageal, M, Inc	–0.71, 0.001 Fruit			0.48, 15, 0.001
Esophageal, M, Mor	–0.82, * Fruit			0.65, 31, *
Esophageal, M, Mor/Inc	7.52, 0.01 Lat*Lat	–7.06, 0.02 Latitude		0.41, 6.6, 0.01
Esophageal, M, Mor/Inc	7.92, 0.009 Lat*Lat	–7.34, 0.01 Latitude	–0.30, 0.17 Alcohol 93	0.46, 5.5, 0.01
Esophageal, F, Inc	–0.75, 0.001 T_{max}			0.53, 19, 0.001
Esophageal, F, Mor	–0.75, 0.001 T_{max}			0.53, 19, 0.001
Esophageal, F, Mor/Inc	–0.81, 0.02 T_{max}	–0.72, 0.03 AE/TE		0.26, 3.9, 0.05
Lung, M, Mor/Inc,	5.66, 0.05 Lat*Lat	–5.07, 0.07 Latitude		0.44, 7.2, 0.007
NHL, M, Inc	0.58, 0.04 AE/TE	–0.45, 0.10 Lat*Lat		0.19, 2.8, 0.09
NHL, M, Mor	0.67, 0.02 AE/TE	–0.23, 0.36 Lat*Lat		0.25, 3.7, 0.05
NHL, M, Mor/Inc	6.89, 0.02 Lat*Lat	–6.36, 0.03 Latitude		0.43, 7.0, 0.008
NHL, M, Mor/Inc	8.62, 0.001 Lat*Lat	–8.02, 0.002 Latitude	(NZ omitted)	0.65, 15, *
NHL, F, Mor	0.70, 0.009 AE/TE	–0.29, 0.24 Latitude		0.31, 4.5, 0.03
NHL, F, Mor/Inc	7.92, 0.005 Lat*Lat	–7.33, 0.008 Latitude	(NZ omitted)	0.59, 12, 0.001

continued

Table II. *continued.*

Cancer, gender	First term (β, *p*)	Second term (β, *p*)	Third term (β, *p*)	Adjusted R^2, F, *p*
NHL, F, Mor/Inc	3.45, 0.26 Lat*Lat	–2.73 Latitude		0.48, 8.0, 0.005
Ovarian, Inc	0.66, * Lat*Lat	0.38, 0.01 AE/TE		0.79, 31, *
Ovarian, Mor	0.69, * Lat*Lat	0.34, 0.03 AE/TE		0.78, 30, *
Ovarian, Mor	3.8, 0.03 Lat*Lat	0.28, 0.04 AE/TE	–3.1, 0.06 Latitude	0.82, 26, *
Ovarian, Mor/Inc	7.04, 0.01 Lat*Lat	–6.46, 0.02 Latitude		0.51, 9.3, 0.003
Pancreatic, M, Mor	0.56, 0.02 Latitude			0.26, 6.8, 0.02
Pancreatic, M, Mor/Inc	0.61, 0.009 Latitude			0.33, 8.9, 0.009
Renal, M, Inc	0.84, 0.01 AE/TE	0.62, 0.06 T_{max}		0.27, 3.9, 0.05
Renal, M, Mor	0.48, 0.04 AE/TE	0.37, 0.10 Lat*Lat		0.48, 8.3, 0.004
Renal, M, Mor/Inc	0.76, * Latitude			0.54, 20, *
Renal, F, Inc	0.76, 0.005 AE/TE	–0.28, 0.23 Lat*Lat		0.37, 5.8, 0.02
Renal, F, Mor	0.47, 0.05 AE/TE	0.35, 0.13 Lat*Lat		0.44, 7.2, 0.007
Renal, F, Mor/Inc	0.77, * Lat*Lat			0.57, 22, *

*$p<0.001$; Inc = incidence; Mor = mortality; NHL: non-Hodgkin's lymphoma. Port out = Portugal omitted from the analysis; Lat*Lat = latitude times latitude.

Discussion

Incidence and mortality data

Ovarian cancer. Latitude plays the most important role in incidence, mortality and apparent survival rates for ovarian cancer. Diet, expressed as the fraction of energy derived from animal products, played only a minor role. Ovarian cancer was one of the first cancers for which an inverse correlation was found between mortality rates and solar UVB irradiance (23), confirmed by later studies (4, 5). What is interesting is that the survival rate increased with latitude between 45 and 56˚ and then decreased above 58˚.

Renal cancer. For renal cancer, dietary factors were found more important than latitude for incidence and mortality, and, in fact, there was little latitudinal variation. However, for survival, latitude was the only significant factor. The latitudinal variation in survival was similar to that for ovarian cancer. Other studies have found vitamin D to be associated with renal cancer risk (4, 53). It should be noted that the kidneys play an important role in converting 25(OH)D to 1,25-dihydroxyvitamin D (1,25(OH)D) (54).

Breast cancer. Diet had the strongest association with breast cancer incidence, whereas latitude had the strongest correlation with mortality and survival rates. Breast cancer mortality rates have often been found to be inversely correlated with solar UVB irradiance (4, 5, 11, 19, 20, 22). Diet has often been found to be an important risk factor for breast cancer (39, 55, 56). In a previous ecologic study, the fraction of energy derived from animal products was found to be the strongest risk factor, with alcohol a significant risk factor and fish a significant risk reduction factor, while latitude was weakly correlated with risk (38).

Esophageal cancer. It is not clear why the esophageal cancer incidence and mortality rates and apparent survival rates for females were inversely correlated with the maximum temperature in July. It could be due to other confounding factors. Dietary vitamin D was found to be inversely correlated with esophageal cancer risk (56), while fruit was found to be protective against esophageal cancer (57, 58), in agreement with the results in Table II.

Lung cancer. The regression results for male lung cancer survival were consistent with a beneficial effect. It is

Table III. *Regression results for 1- and 5-year survival rates vs. second order function of latitude for nine West European countries with population centers between 40° and 56° N.*

Cancer, gender, Survival rate	Lat*Lat (β, *p*)	Latitude (β, *p*)	AE/ TE 85	Adjusted r^2, F, *p*
All, M, 1 yr	–14.9, 0.03	14.6, 0.04		0.45, 4.2, 0.07
All, M, 1 yr	–13.8, 0.02	13.0, 0.03	0.67, 0.07	0.67, 6.5, 0.04
All, M, 5 yr	–13.2, 0.06	12.9, 0.07		0.36, 3.2, 0.11
All, F, 1 yr	–13.6, 0.04	13.2, 0.04		0.51, 5.1, 0.05
All, F, 1 yr	–12.7, 0.04	11.9, 0.04	0.55, 0.14	0.63, 5.6, 0.05
All, F, 5 yr	–12.5, 0.04	12.0, 0.04		0.58, 6.4, 0.03
All, F, 5 yr	–11.7, 0.03	10.7, 0.05	0.52, 0.13	0.69, 7.0, 0.03
Breast, 5 yr	–0.62, 0.07			0.30, 4.4, 0.07
Colon, M, 1 yr	–14.1, 0.02	13.6, 0.02		0.63, 7.9, 0.02
Colon, M, 5 yr	–11.9, 0.02	11.2, 0.03		0.73, 12, 0.009
Colon, M, 5 yr	–11.2, 0.02	10.3, 0.03	0.37, 0.18	0.78, 10, 0.01
Colon, F, 5 yr	–12.6, 0.05	12.1, 0.05		0.52, 5.4, 0.05
Colon, F, 5 yr	–11.7, 0.05	10.8, 0.06	0.52, 0.16	0.63, 5.6, 0.05
Gastric, M, 1 yr	–12.1, 0.03	11.5, 0.04		0.65, 8.5, 0.02
Gastric, M, 5 yr	–8.3, 0.08	7.5, 0.11		0.70, 10.5, 0.01
Gastric, F, 1 yr	–12.4, 0.02	11.7, 0.02		0.72, 11, 0.01
Gastric, F, 5 yr	–11.3, 0.04	10.7, 0.05		0.64, 8.2, 0.02
Lung, M, 1 yr	–13.6, 0.04	13.2, 0.05		0.48, 4.7, 0.06
Lung, F, 1 yr	–13.8, 0.02	13.3, 0.03		0.61, 7.2, 0.03
Lung, F, 5 yr	–14.8, 0.01	14.3, 0.01		0.68, 9.3, 0.01
Pancreatic, M, 1 yr	–14.9, 0.01	14.4, 0.01		0.67, 9.2, 0.02
Pancreatic, F, 1 yr	–12.5, 0.05	12.0, 0.06		0.49, 4.8, 0.06
Prostate, 1 yr	–16.0, 0.02	15.8, 0.02		0.52, 5.3, 0.05
Prostate, 5 yr	–15.6, 0.01	15.2, 0.01		0.64, 8.0, 0.02
Renal, M, 5 yr	–13.1, 0.04	12.6, 0.04		0.56, 6.0, 0.04
Renal, F, 5 yr	–11.2, 0.07	10.7, 0.08		0.50, 5.0, 0.05

Graphs of cancer incidence, mortality and mortality divided by incidence rate using data for 2002.

puzzling that the survival rate was greater than unity for three of the Nordic countries. Reductions in smoking rates during the past two decades might have been greater in the Nordic countries than in the other countries. This hypothesis is supported by looking at the correlation between the ratio of per capita cigarette smoking averaged for 1990 and 2000 *versus* that for 1980 (59). There was a strong correlation when the Nordic countries were included but not when they were excluded. However, it is noted that when the Nordic countries were excluded from the analysis, there was still a strong correlation between survival and decreasing latitude. Vitamin D from solar UVB irradiance and oral intake were found to be strongly correlated with 5-year survival from non-small cell lung cancer in a case-control study in Boston (10).

Non-Hodgkin's lymphoma. For NHL, only latitude was found significantly associated with risk. Solar UVB has been found inversely correlated with risk (3, 60-62). However, latitude has also been found inversely correlated with the risk of developing NHL in Sweden (63), although solar UV irradiance was not necessarily implicated. Another study in Sweden found a 30% (95% confidence interval = 0.9 to 1.9) increased risk of NHL for a high solar-exposure group (64). Although survival from Hodgkin's lymphoma was found to be increased for diagnosis in the fall in Norway, attributed to increased vitamin D production in the summer (8), no seasonal variation of survival was found for NHL (Porojnicu, private communication). A review of the literature on the risk of skin cancer (melanoma and basal cell carcinoma) development among those with NHL concluded that there was a significant risk (65). It is noted that UVA (wavelength = 315–400 nm) appeared more strongly correlated with melanoma (66) and basal cell carcinoma (67) than UVB. Immune suppression is thought to play an important role in the etiology of NHL (68, 69). Thus, there is reason to suspect that UVA, through immunosuppression (70), plays a role in the etiology of NHL.

It was noted that the latitudinal variation of NHL survival rates continued to increase in the Nordic countries, in contrast to the results for the other three cancers. This provides further support for the UVA/immunosuppression hypothesis since the ratio of UVA to UVB irradiance increases with increasing latitude (71).

Other cancers. The regression results for colorectal cancer found that dietary factors were much more important than latitude. Diet has been found to play an important role in the etiology of colon cancer (72).

EUROCARE-3 data. The results for 1- and 5-year survival rates using EUROCARE-3 data also provided support for the hypothesis that solar UVB, through production of vitamin D, improves the survival rate once the cancer has reaches the stage where it is discovered. In most of the results tabulated in Table III, the highest survival rates were found in Austria, France and Switzerland, countries situated between 42°N and 51°N. The French generally go on vacation in August, and both Austria and Switzerland have many high mountains. Italians and Spaniards have slightly darker skin than Europeans to the north (35) and so would produce less vitamin D from the same amount of UVB. Denmark and England have the lowest cancer survival rates, with 5-year survival for all cancers of 36% for males and 48% for females *versus* 45%–55% for males and 58% for females in Austria, France and Switzerland. The level of medical care in the various countries may contribute to the results, but the fact that statistically significant correlations with a quadratic function of latitude were found only for cancers shown to be vitamin D sensitive in other studies (4, 10, 25, 26) suggests that the effect of health care is smaller than the UVB–vitamin D effect.

The results for the datasets are similar but with some differences. In both cases, there was little variation for latitudes less than 50˚, then a decrease in apparent or actual survival rates between 50˚ and 56˚, followed by survival rates for the Nordic countries near those/that for countries between 40˚ and 52˚. Some cancers were found to be vitamin D-sensitive by both approaches, whereas for others, only one approach gave that indication. Although different countries were studied, using mortality divided by incidence data for the nine countries only did not greatly change the results compared to if all 17 countries had been used. The results using actual survival data are very likely more reliable than those using the ratio of mortality to incidence. However, use of the ratio allows more countries to be included in the analysis, thus enabling a wider range of latitude and other factors to be employed.

Molecular mechanisms. The key processes whereby vitamin D plays an important role in the reduction of cancer incidence and death is the conversion of 25(OH)D to 1,25(OH)$_2$D in the organs that can benefit from the hormonal version of vitamin D followed by attachment to vitamin D receptors (VDRs). This conversion step was first demonstrated in colon cancer cells by Cross *et al.* (73) and extended to many organs by Zehnder *et al.* (74). It was also shown in further laboratory studies that more 1,25(OH)$_2$D was produced as tumors progress (75-78). The role of VDRs has been explored in several studies (79). The mechanisms whereby vitamin D reduces the risk of cancer include increasing cell differentiation and apoptosis, reducing angiogenesis around tumors and reducing metastasis (80, 81).

Dietary factors. Dietary and lifestyle factors such as smoking seem to be more important in cancer etiology prior to discovery, with vitamin D playing a more important role relative to dietary and lifestyle factors after cancer reaches the stage where it can be detected. This supposition is in agreement with the recent report that a vitamin D index correlated better with mortality rates than incidence rates in the Health Professionals Follow-Up Study cohort (9).

Although several studies have not found an inverse correlation between dietary vitamin D and colorectal cancer or adenomas, which has been attributed to values insufficient to have a significant impact (5), unmodeled factors, such as dietary factors and alcohol consumption, might have masked the vitamin D effect at low vitamin D intake levels.

Alternative possibilities for the latitudinal variation in cancer rates. It was assumed, in this work, that latitude is an index of vitamin D variation from solar UVB irradiance. However, there are other factors that vary with latitude including genetic factors such as skin pigmentation (35), which would affect the vitamin D production rate, and apolipoprotein E (APOE) epsilon 4 allele frequency in the population. The prevalence of the APOE epsilon 4 allele, which increases the production of fat from food, increases with latitude in Europe (82).

Another possibility is that screening for some cancers, such as breast, colorectal and prostate, could be higher in some countries, and this would lead to a latitudinal gradient in cancer incidence, mortality and survival. However, there are reports that screening is not very effective in reducing cancer mortality rates, although screening does increase incidence rates. Fecal occult blood testing and colonoscopy seem to be cost-effective ways of reducing colon cancer (83). However, meta-analyses of the benefits of mammography in reducing the mortality rates for breast cancer indicated that the benefits are minimal at best (84, 85). The results for prostate-specific antigen (PSA) were also inconclusive (86). An ecologic study in the United States suggested a reduced mortality rate for prostate cancer associated with PSA screening (87). When July UVB, measured using the Total Ozone Mapping Spectrometer (TOMS) (28) and latitude, an index for wintertime serum 25(OH)D, were included in the model with incidence and mortality rate data, the correlation with PSA testing was insignificant (Grant, unpublished).

Regardless of the effectiveness of screening in reducing cancer mortality rates, further information would be required on screening rates and practices in the various countries to determine whether they are used at different rates that vary with latitude. Also, since there is no screening for gastric, ovarian, pancreatic and renal cancer and NHL, and since they show strong latitudinal survival gradients, it is unlikely that screening explains the results for colorectal or prostate cancer in the datasets used here. However, different screening practices may explain the low latitudinal variation in breast cancer survival.

Conclusion

There are several conclusions that can be drawn from this study. One is that vitamin D seems to play a more important role in fighting cancer once it has developed to the point of detection rather than in preventing it from starting. Cancer is generally considered to go through three phases: initiation, progression and metastasis. Since initiation is due to risk factors, vitamin D may not be involved in this phase other than to inhibit initiation. Although vitamin D has mechanisms that play a role in all phases, there may be fewer other natural factors fighting cancer as it progresses and metastasizes, so the relative impact may be higher.

A second conclusion is that 25(OH)D levels should be measured for most people diagnosed with cancer (18 types have been identified as vitamin D-sensitive (4,26,27)) and, if low, these people should receive vitamin D supplements. Organs that can use 1,25(OH)$_2$D in fighting cancer can convert 25(OH)D to 1,25(OH)$_2$D (73, 74). Daily oral intakes of 2000 IU (50 μg) are considered safe, and intakes up to 4000 IU/day are probably safe (88). Although there is an interest in the development of analogs of 1,25(OH)$_2$D for the treatment of cancer since they would have the benefits of natural 1,25(OH)$_2$D without the adverse hypercalcemic effects (89, 90), it seems that first priority should be given to exploring the potential of natural vitamin D to treat cancer.

A third conclusion is that the higher levels of dietary and supplemental vitamin D found in the Nordic countries apparently do have an important impact on cancer mortality rates. Those in Northern Europe have lower fractions of elderly with low serum 25(OH)D levels in winter (51, 91, 92). It seems especially important to institute vitamin D fortification programs in the rest of Europe where vitamin D levels are low (51). Thus, efforts to increase vitamin D fortification, such as adding vitamin D to bread (93, 94), are encouraged.

It is noted that the health benefits of increased vitamin D extend far beyond cancer to other diseases and conditions such as bone health (95), muscle health (96), reduced risk of multiple sclerosis (97) and blood pressure (98). There are several reviews on the health benefits of vitamin D (99-106).

It is hoped that interest in the role of vitamin D in reducing the risk of cancer incidence and mortality will continue to increase and that clinical studies designed to determine dose-response relations will be conducted.

References

1 Doll R and Peto R: The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst *66*: 1191-1308, 1981.

2 World Cancer Research Fund in association with the American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a global perspective. Wash., DC, pp. 670, 1997

3 Grant WB: An estimate of premature cancer mortality in the United States due to inadequate doses of solar ultraviolet-B radiation. Cancer *94*: 1867-1875, 2002.

4 Freedman DM, Dosemeci M and McGlynn K: Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med *51*: 257-262, 2002.

5 Grant WB and Garland CF: A critical review of studies on vitamin D in relation to colorectal cancer. Nutr Cancer *48*: 115-123, 2004.

6 Robsahm TE, Tretli S, Dahlback A and Moan J: Vitamin D_3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control *15*: 149-158, 2004.

7 Moan J, Porojnicu AC, Robsahm TE *et al*: Solar radiation, vitamin D and survival rate of colon cancer in Norway. J Photochem Photobiol B *78*: 189-193, 2005.

8 Porojnicu AC, Robsahm TE, Ree AH and Moan J: Season of diagnosis is a prognostic factor in Hodgkin's lymphoma: a possible role of sun-induced vitamin D. Br J Cancer *93*: 571-574, 2005.

9 Giovannucci E: The role of vitamin D in cancer incidence and prevention. Am Assoc Cancer Res Annual Meeting, 2005.

10 Zhou W, Suk R, Liu G, Park S, Neuberg DS, Wain JC, Lynch TJ, Giovannucci E and Christiani DC: Vitamin D is associated with improved survival in early-stage non-small cell lung cancer patients. Cancer Epidemiol Biomarkers Prev *14*: 2303-2309, 2005.

11 Grant WB: Lower vitamin-D production from solar ultraviolet-B irradiance may explain some differences in cancer survival rates. J Natl Med Assoc *98*: 357-364, 2006.

12 Morgenstern H: Ecologic studies. *In*: Modern Epidemiology, 2nd Edition (Rothman KJ, Greenland S, eds.). Lippincott, Philadelphia, pp. 459-480, 1998.

13 Greenland S: Ecologic *versus* individual-level sources of confounding in ecologic estimates of contextual health effects. Int J Epidemiol *30*: 1343-1350, 2001.

14 Hill AB: The environment and disease: association or causation? Proc R Soc Med *58*: 295-300, 1965.

15 Weed DL: Environmental epidemiology: basics and proof of cause-effect. Toxicology *181-182*: 399-403, 2002.

16 Garland CF and Garland FC: Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol *9*: 227-231, 1980.

17 Garland C, Shekelle RB, Barrett-Connor E *et al*: Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet *1*: 307-309, 1985.

18 Gorham ED, Garland CF and Garland FC: Acid haze air pollution and breast and colon cancer mortality in 20 Canadian cities. Can J Public Health *80*: 96-100, 1989.

19 Gorham ED, Garland FC and Garland CF: Sunlight and breast cancer incidence in the USSR. Int J Epidemiol *19*: 820-824, 1990.

20 Garland CF, Comstock GW and Garland FC *et al*: Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet *2*: 1176-1178, 1989.

21 Garland FC, Garland CF, Gorham ED and Young JF: Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med *19*: 614-622, 1990.

22 Lefkowitz ES and Garland CF: Sunlight, vitamin D, and ovarian cancer mortality rates in US women. Int J Epidemiol *23*: 1133-1136, 1994.

23 Hanchette CL and Schwartz GG: Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. Cancer *70*: 2861-2869, 1992.

24 Devesa SS, Grauman DJ, Blot WJ *et al*: Atlas of Cancer Mortality in the United States, 1950-1994. NIH Publication No. 99-4564, 1999. http://cancer.gov/atlasplus/new.html (accessed Sept. 21, 2005).

25 Grant WB: Benefits of UVB exposure to reduce the risk of cancer – ecologic studies of cancer mortality rates. Proceedings of the CIE Symposium '04; Light and Health: Non-visual Effects, 30 Sep.-2 Oct. 2004, Commission International de L'Eclairage, pp. 174-177, 2004.

26 Grant WB: Ecologic studies of solar UV-B radiation and cancer mortality rates. Rec Results Cancer Res *164*: 371-377, 2003.

27 Grant WB and Garland CF: Association of solar ultraviolet B with reduced mortality rates of some types of cancer: multifactorial ecologic study. Poster presentation at the annual meeting of the American Association for Cancer Research, Anaheim, April 18, 2005 (available at www.sunarc.org)

28 Leffell DJ and Brash DE: Sunlight and skin cancer. Sci Am *275*: 52-53, 56-59, 1996. http://toms.gsfc.nasa.gov/ery_uv/ dna_exp.gif (accessed Sept. 21, 2005).

29 Nutrition Monitoring Div., Human Nutrition Information Service, U.S. Dept. of Agriculture, Food and Nutrient Intakes: Individuals in Four Regions, Year 1977-78, Hyattsville, MD, Report No. I-3, 1985.
30 Grant WB: Geographic variation of prostate cancer mortality rates in the United States: implications for prostate cancer risk related to vitamin D. Int J Cancer *111*: 470-471, 2004.
31 Tuohimaa P, Tenkanen L, Ahonen M *et al*: Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer *108*: 104-108, 2004.
32 Ferlay J, Bray F, Pisani P and Parkin DM: GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5. version 2.0, IARCPress, Lyon, 2004. http://www-dep.iarc.fr/ (accessed Sept. 22, 2005).
33 Sant M, Aareleid T, Berrino F *et al*: EUROCARE-3: survival of cancer patients diagnosed 1990-94 – results and commentary. Ann Oncol *14*: v61-v118, 2003.
34 Capocaccia R, Gatta G, Roazzi P *et al*: The EUROCARE-3 database: methodology of data collection, standardisation, quality control and statistical analysis. Ann Oncol *14*: v14-v27, 2003.
35 Jablonski NG and Chaplin G: The evolution of human skin coloration. J Hum Evol *39*: 57-106, 2000.
36 FAOSTAT data, 2005. Last update 27 August 2004 http://faostat.fao.org/faostat/ (accessed Sept. 22, 2005).
37 Tsuji K, Harashima E, Nakagawa Y *et al*: Time-lag effect of dietary fiber and fat intake ratio on Japanese colon cancer mortality. Biomed Environ Sci *9*: 223-228, 1996.
38 Grant WB: An ecologic study of dietary and solar UV-B links to breast carcinoma mortality rates. Cancer *94*: 272-281, 2002.
39 Huncharek M and Kupelnick B: Dietary fat intake and risk of epithelial ovarian cancer: a meta-analysis of 6,689 subjects from 8 observational studies. Nutr Cancer *40*: 87-91, 2001.
40 Zheng T, Holford TR, Leaderer B *et al*: Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut women. Am J Epidemiol *159*: 454-466, 2004.
41 Rashidkhani B, Akesson A, Lindblad P and Wolk A: Major dietary patterns and risk of renal cell carcinoma in a prospective cohort of Swedish women. J Nutr *135*: 1757-1762, 2005.
42 Jacobs DR Jr, Marquart L, Slavin J and Kushi LH: Whole-grain intake and cancer: an expanded review and meta-analysis. Nutr Cancer *30*: 85-96, 1998.
43 Riboli E and Norat T: Cancer prevention and diet: opportunities in Europe. Public Health Nutr *4*: 475-484, 2001.
44 Shannon J, Cook LS and Stanford JL: Dietary intake and risk of postmenopausal breast cancer (United States). Cancer Causes Control *14*: 19-27, 2003.
45 Fritschi L, Ambrosini GL, Kliewer EV *et al*: Dietary fish intake and risk of leukaemia, multiple myeloma, and non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev *13*: 532-537, 2004.
46 Giovannucci E: Nutrition, insulin, insulin-like growth factors and cancer. Horm Metab Res *35*: 694-704, 2003.
47 Kaaks R: Endogenous hormone metabolism as an exposure marker in breast cancer chemoprevention studies. IARC Sci Publ *154*: 149-162, 2001.
48 Yu H, Shu XO, Li BD *et al*: Joint effect of insulin-like growth factors and sex steroids on breast cancer risk. Cancer Epidemiol Biomarkers Prev *12*: 1067-1073, 2003.
49 Mandelson MT, Miglioretti D, Newcomb PA *et al*: Hormone replacement therapy in relation to survival in women diagnosed with colon cancer. Cancer Causes Control *14*: 979-984, 2003.
50 Bruce WR, Giacca A and Medline A: Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol Biomarkers Prev *9*: 1271-1279, 2000.
51 van der Wielen RP, Lowik MR, van den Berg H *et al*: Serum vitamin D concentrations among elderly people in Europe. Lancet *346*: 207-210, 1995.
52 SPSS 13.0 Brief Guide, SPSS Inc., Chicago, 2004.
53 Ikuyama T, Hamasaki T, Inatomi H *et al*: Association of vitamin D receptor gene polymorphism with renal cell carcinoma in Japanese. Endocr J *49*: 433-438, 2002.
54 Holick MF: Vitamin D for health and in chronic kidney disease. Semin Dial *18*: 266-275, 2005.
55 Cho E, Spiegelman D, Hunter DJ *et al*: Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst *95*: 1079-1085, 2003.
56 Launoy G, Milan C, Day NE *et al*: Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. Int J Cancer *76*: 7-12, 1998.
57 Onuk MD, Oztopuz A and Memik F: Risk factors for esophageal cancer in eastern Anatolia. Hepatogastroenterology *49*: 1290-1292, 2002.
58 De Stefani E, Boffetta P, Deneo-Pellegrini H *et al*: The role of vegetable and fruit consumption in the aetiology of squamous cell carcinoma of the oesophagus: a case-control study in Uruguay. Int J Cancer *116*: 130-135, 2005.
59 Shafey O, Dolwick S and Guindon GE (eds.): Tobacco Control Country Profiles, Second Edition, 2003. American Cancer Society, World Health Organization, and International Union Against Cancer. http://www.wpro.who.int/NR/rdonlyres/437C3114-24FE-45CA-9A62-8E119BC66CC6/0/TCCP2.pdf (accessed September 8, 2005).
60 Hu S, Ma F, Collado-Mesa F and Kirsner RS: Ultraviolet radiation and incidence of non-Hodgkin's lymphoma among Hispanics in the United States. Cancer Epidemiol Biomarkers Prev *13*: 59-64, 2004.
61 Hughes AM, Armstrong BK, Vajdic CM *et al*: Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. Int J Cancer *112*: 865-871, 2004.
62 Smedby KE, Hjalgrim H, Melbye M *et al*: Ultraviolet radiation exposure and risk of malignant lymphomas. J Natl Cancer Inst *97*: 199-209, 2005.
63 Adami J, Gridley G, Nyren O *et al*: Sunlight and non-Hodgkin's lymphoma: a population-based cohort study in Sweden. Int J Cancer *80*: 641-645, 1999.
64 Hakansson N, Floderus B, Gustavsson P *et al*: Occupational sunlight exposure and cancer incidence among Swedish construction workers. Epidemiology *12*: 552-557, 2001.
65 Hu S, Federman DG, Ma F and Kirsner RS: Skin cancer and non-Hodgkin's lymphoma: examining the link. Dermatol Surg *31*: 76-82, 2005.
66 Moan J, Dahlback A and Setlow RB: Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. Photochem Photobiol *70*: 243-247, 1999.
67 Green A, Williams G, Neale R *et al*: Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet *354*: 723-729, 1999.

68 Fisher SG and Fisher RI: The epidemiology of non-Hodgkin's lymphoma. Oncogene *23*: 6524-6534, 2004.
69 Brennan P, Scelo G, Hemminki K *et al*: Second primary cancers among 109,000 cases of non-Hodgkin's lymphoma. Br J Cancer *93*: 159-166, 2005.
70 Ullrich SE. Mechanisms underlying UV-induced immune suppression. Mutat Res *571*: 185-205, 2005.
71 Garland CF, Garland FC and Gorham ED: Epidemiologic evidence for different roles of ultraviolet A and B radiation in melanoma mortality rates. Ann Epidemiol *13*: 395-404, 2003.
72 Grant WB: Dietary fiber and colorectal cancer. Townsend Lett *192*: 112-113, 1999.
73 Cross HS, Peterlik M, Reddy GS and Schuster I: Vitamin D metabolism in human colon adenocarcinoma-derived Caco-2 cells: expression of 25-hydroxyvitamin D3-1alpha-hydroxylase activity and regulation of side-chain metabolism. J Steroid Biochem Mol Biol *62*: 21-28, 1997.
74 Zehnder D, Bland R, Williams MC *et al*: Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metab *86*: 888-894, 2001.
75 Cross HS, Bareis P, Hofer H *et al*: 25-Hydroxyvitamin D(3)-1alpha-hydroxylase and vitamin D receptor gene expression in human colonic mucosa is elevated during early cancerogenesis. Steroids *66*: 287-292, 2001.
76 Bareis P, Bises G, Bischof MG *et al*: 25-Hydroxy-vitamin D metabolism in human colon cancer cells during tumor progression. Biochem Biophys Res Commun *285*: 1012-1017, 2001.
77 Bises G, Kallay E, Weiland T *et al*: 25-Hydroxyvitamin D3-1alpha-hydroxylase expression in normal and malignant human colon. J Histochem Cytochem *52*: 985-989, 2004.
78 Kallay E, Bises G, Bajna E *et al*: Colon-specific regulation of vitamin D hydroxylases – a possible approach for tumor prevention. Carcinogenesis *26*: 1581-1589, 2005.
79 Peterlik M and Cross HS: Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest *35*: 290-304, 2005.
80 van den Bemd GJ and Chang GT: Vitamin D and vitamin D analogs in cancer treatment. Curr Drug Targets *3*: 85-94, 2002.
81 Krishnan AV, Peehl DM and Feldman D: The role of vitamin D in prostate cancer. Rec Results Cancer Res *164*: 205-221, 2003.
82 Lucotte G, Loirat F and Hazout S: Pattern of gradient of apolipoprotein E allele *4 frequencies in western Europe. Hum Biol *69*: 253-262, 1997.
83 Vijan S, Hwang EW, Hofer TP and Hayward RA: Which colon cancer screening test? A comparison of costs, effectiveness, and compliance. Am J Med *111*: 593-601, 2001.
84 Gotzsche PC and Olsen O: Is screening for breast cancer with mammography justifiable? Lancet *355*: 129-134, 2000.
85 Green BB and Taplin SH: Breast cancer screening controversies. J Am Board Fam Pract *16*: 233-241, 2003.
86 Gibbons L and Waters C: Prostate cancer – testing, incidence, surgery and mortality. Health Rep *14*: 9-20, 2003.
87 Jemal A, Ward E, Wu X *et al*: Geographic patterns of prostate cancer mortality and variations in access to medical care in the United States. Cancer Epidemiol Biomarkers Prev *14*: 590-595, 2005.
88 Vieth R: Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr *69*: 842-856, 1999.
89 Banerjee P and Chatterjee M: Antiproliferative role of vitamin D and its analogs – a brief overview. Mol Cell Biochem *253*: 247-254, 2003.
90 Beer TM and Myrthue A: Calcitriol in cancer treatment: from the lab to the clinic. Mol Cancer Ther *3*: 373-381, 2004.
91 Rasmussen LB, Hansen GL, Hansen E *et al*: Vitamin D: should the supply in the Danish population be increased? Int J Food Sci Nutr *51*: 209-215, 2000.
92 Ovesen L, Andersen R and Jakobsen J: Geographical differences in vitamin D status, with particular reference to European countries. Proc Nutr Soc *62*: 813-821, 2003.
93 Newmark HL, Heaney RP and Lachance PA: Should calcium and vitamin D be added to the current enrichment program for cereal-grain products? Am J Clin Nutr *80*: 264-270, 2004.
94 Mocanu V, Stitt PA, Costin AR *et al*: Long-term efficacy and safety of high vitamin D intakes as fortified bread. Experimental Biology 2005 meeting. April 2. San Diego. Abstract available at http://www.eb2005-online.com/pdfs/009665.PDF?PHPSESSID=1c3b0454d98b47ca5a0cbd6c57920.
95 Malabanan AO and Holick MF: Vitamin D and bone health in postmenopausal women. J Womens Health (Larchmt) *12*: 151-156, 2003.
96 Plotnikoff GA and Quigley JM: Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc *78*: 1463-1470, 2003.
97 Cantorna MT and Mahon BD: Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med (Maywood) *229*: 1136-1142, 2004.
98 Li YC, Qiao G, Uskokovic M *et al*: Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol *89-90*: 387-392, 2004.
99 Heaney RP: Long-latency deficiency disease: insights from calcium and vitamin D. Am J Clin Nutr *78*: 912-919, 2003.
100 Holick MF: Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr *79*: 362-371, 2004.
101 Holick MF: Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr *80*: 1678S-1688S, 2004.
102 Mosekilde L: Vitamin D and the elderly. Clin Endocrinol (Oxf) *62*: 265-281, 2005.
103 Ponsonby AL, Lucas RM and van der Mei IA: UVR, vitamin D and three autoimmune diseases – multiple sclerosis, type 1 diabetes, rheumatoid arthritis. Photochem Photobiol *81*: 1267-1275, 2005,
104 Grant WB and Holick MF: Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev *10*: 94-111, 2005.
105 Grant WB, Garland CF and Holick MF: Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. Photochem Photobiol *81*: 1276-1286, 2005.
106 Staud R: Vitamin D: more than just affecting calcium and bone. Curr Rheumatol Rep *7*: 356-364, 2005.

Received December 29, 2005
Accepted January 14, 2006